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CIBA-GEIGY

Attachment A

December 9, 1982

6 pg

Mr. Richard F. Mountfort
Product Manager (23)
Registration Division (TS-767C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Mr. Mountfort:

SUBJECT: METOLACHLOR HERBICIDE
RISK ASSESSMENT BASED ON THE REPEAT
2-YEAR RAT STUDY

As you are aware, CIBA-GEIGY agreed to repeat a 2-year rat study on metolachlor when agency scientists determined that the original IBTL study did not meet the core minimum classification. The in-life phase of that study was completed earlier this year and the histopathology evaluation of the livers on the repeat 2-year rat study on metolachlor technical performed at Hazelton-Raltech, Inc., Madison, Wisconsin has been recently completed. In the repeat study, as in the original IBTL study, certain liver lesions appeared to result from the administration of metolachlor. Additional evaluations are planned in this study.

A repeat 2-year mouse study recently submitted to EPA did not indicate any oncogenic potential of metolachlor, as with the initial mouse study. Therefore, the rat liver response is considered a very weak species-specific lesion.

At this time, low dose extrapolation to evaluate the potential risk to humans with respect to these findings is considered inappropriate. If it were essential to perform risk assessment after all evaluations are completed with respect to the repeat rat study, the data employed should be the number of animals bearing proliferative lesions of the hepatocytes. These data are presented on the following page.

Incidence

Lesion	Sex	Feeding Level (PPM) 0	30	300	3000
Proliferative Foci (Neoplastic Nodule)	M	0 0	2 0	0 0	6 4
	F	0 0	1 0	1 1	5 4
Hepatocellular (Carcinoma)	M	2 2	0 1	2 3	3 2
	F	0 0	0 0	1 0	2 2
Total Animals with Lesions	M	2 2	2 1	2 3	9 6
	F	0 0	1 0	2 1	7 6
Total Animals Examined	M	60 59	57 59	60 60	60 60
	F	59 60	60 60	59 60	60 60

Based upon the computer model of Crump, the coefficients of the polynomials that best fit the data for the multi-stage model are:

Male Data:
$Q(0) = 3.444 \times 10^{-2}$
$Q(1) = 0$
$Q(2) = 0$
$Q(3) = 4.743 \times 10^{-12}$

Female Data:
$Q(0) = 9.916 \times 10^{-3}$
$Q(1) = 4.081 \times 10^{-5}$
$Q(2) = 0$
$Q(3) = 0$

Exposure

Potential Theoretical Maximum Residue Concentration (TMRC) for established and proposed tolerances are based on tolerances, percent of diet and percent acreage treated. These are shown below for metolachlor.

Established Tolerances

Consumed Commodities	Tolerances	% of Diet	% of Acreage Treated*	TMRC mg/day/ 1.5 kg food
Sorghum	0.30	0.03	24.2	3.29×10^{-5}
Corn, Grain	0.10	1.00	18.9	2.84×10^{-4}
Peanuts	0.10	0.36	2.7	1.46×10^{-5}
Soybeans	0.10	0.92	8.6	1.19×10^{-4}
Eggs	0.02	2.77	18.9**	1.57×10^{-4}
Meat: Inc. Poultry	0.02	13.85	18.9**	7.86×10^{-4}
Milk & Dairy Products	0.02	28.62	18.9**	1.62×10^{-3}
Cottonseed	0.10	0.15	0.6	1.38×10^{-6}
Potatoes	0.20	5.43	3.8	6.19×10^{-4}
Corn: Pop	0.10	0.08	18.9	2.27×10^{-5}
Corn: Sweet	0.10	1.43	18.9	4.06×10^{-4}
Seed and Pod Veg.	0.30	3.66	2.3	3.79×10^{-4}
Safflower	0.1	0.03	10	4.50×10^{-6}
Barley (Rotational)	0.1	0.03	2	9.00×10^{-5}
Buckwheat (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Millet Forage (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Milo (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Oat (Rotational)	0.1	0.36	3	1.62×10^{-5}
Rice (Rotational)	0.1	0.55	3	2.48×10^{-5}
Rye (Rotational)	0.1	0.03	< 1	4.50×10^{-7}
Wheat (Rotational)	0.1	10.36	5	7.77×10^{-4}

Total TMRC = 5.36×10^{-3} mg/1.5 kg food
or 3.57 ppb in the diet.

*Based upon 1983 projected sales figures, these are larger figures than the 1982 projections so they represent maximal values.

**The acreage used is that for corn. This assumption is based on corn as the major seed component and the fact that this is one of the larger percentages of acreage treated.

Pending Tolerances

Consumed Commodities	Tolerance	% of Diet	% of Acreage Treated*	TMRC mg/day/ 1.5 kg food
Flax Seed	0.20	0.03	1.3	1.17×10^{-6}
Sunflower	0.30	0.03	1.3	1.82×10^{-6}
Peanuts (High Rate)	0.50	0.36	2.7	7.29×10^{-5}
Soybeans (High Rate)	0.20	0.92	8.6	2.37×10^{-4}

Subtotal TMRC - 3.10×10^{-4} mg/1.5 kg food
or 0.21 ppb in the diet.

The TMRC for all established tolerances plus proposed tolerances would be the combination of the 2 numbers minus the TMRC for low rate peanuts and soybeans:

$5.36 \times 10^{-3} + 3.10 \times 10^{-4} - 1.04 \times 10^{-4}$

$= 5.57 \times 10^{-3}$ mg/1.5 kg food

or

= 3.71 ppb in the diet

Applicator Exposure has been established by R. Honeycutt. These data are presented below:

Mixer/Loader Exposure:

0.515 mg/yr. X 10% absorbed: 365 days/yr X 40 yrs./70 yrs. = 0.0000806 mg/day averaged over a lifetime.

This is equivalent to 0.054 ppb in the diet.

Applicator Exposure:

38.1 mg/yr. X 10% absorbed: 365 days/yr. X 40 yrs./70 yrs. = 0.005965 mg/day average over a lifetime.

This is equivalent to 4.00 ppb in the diet.

Risk Calculations (Based on Repeat Rat Study)

Risk calculations are then based on the modile parameters of worst case (female data) and exposure estimate are presented below:

Present dietary exposure including market share:

Dose .00357 Response: 1.44×10^{-7}
Risk $1/6.93 \times 10^{6}$
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Dietary risk for established and pending tolerances including market share:

Dose .00371 Response: 1.50×10^{-7}
Risk $1/6.67 \times 10^{6}$
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Mixer loader including dietary (10% dermal absorption):

Dose .003764 Response: 1.52×10^{-7}
Risk $1/6.57 \times 10^{6}$
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Applicator including dietary (10% dermal absorption):

Dose .00771 Response: 3.12×10^{-7}
Risk $1/3.21 \times 10^{6}$
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Risk based on mixer loader, applicator and dietary exposure:

Dose .007764 Response: 3.14×10^{-7}
Risk $1/3.19 \times 10^{6}$

These values indicate that even if metolachlor were to present a potential risk to humans, the risk is not unreasonable.

Risk calculations, based on the original IBTL study, were submitted to you on November 11, 1981. Based on the Agency's subsequent internal risk assessment of the original rat study,

tolerances were established for metolachlor residues in cotton, potatoes, seed, and pod vegetables, sweet corn and popcorn, which permitted the March 5, 1982 registration of Dual® 8E for use on these crops. The risk calculations above are substantially the same as those based on the IBTL Study. Therefore, we conclude that the results of the risk assessment on the repeat rat study support the continued usage of metolachlor herbicides as currently registered, as well as proposed expanded usage on corn, soybeans, peanuts, sunflowers and flax.

Further evaluation of these data continue. We expect the final report to be available on or before the September 1983 date agreed upon.

If you have any questions, please call me.

Sincerely,

Gene Holt

Gene Holt, Ph.D.
Senior Regulatory Specialist
Government Affairs

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